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We explored the drug etiology of breast cancer through analyses of data from our hospital-based Case-Control Surveillance Study of medications and cancer. Over 5000 cases of incident breast cancer were included in these analyses. We carried out computer "screens" to detect unsuspected associations, in which the use of each drug or drug class among women with breast cancer was compared with that among women with other conditions. The literature relevant to associations seen in the computer screen was reviewed. Inverse associations with heparin use and phenytoin use and a positive association with clomiphene citrate use may warrant further exploration. The relation of use of nonsteroidal anti-inflammatory drugs to breast cancer risk was assessed in detail and a manuscript was prepared: the results suggest little or no association. A detailed analysis of use of drugs that bind to intracellular histamine receptors in relation to breast cancer risk was conducted and a manuscript was prepared. There was a weak positive association of breast cancer risk with use of the newest class of antidepressants, the selective seratonin uptake inhibitors, but the results were not statistically significant. The use of tricyclic antidepressants, other antidepressants, phenothiazines, and antihistamines was unrelated to risk.

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Lynn Rosenberg Aug 26, 1998

PI - Signature Date

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INTRODUCTION

Several drugs have been involved in the etiology of cancer. For example, postmenopausal estrogen supplements are associated with an increased risk of endometrial cancer.[1] It is possible that drugs might be involved in the etiology of breast cancer as well. Oral contraceptive use[2] and postmenopausal female hormone use[3] have been assessed, but there has not been a systematic assessment of other drugs that might be associated with the risk of breast cancer. The purpose of the present study was to begin such a systematic assessment, through analyses of data from our Case-Control Surveillance Study of drugs and cancer.

In the first year of the present grant, we carried out computer "screens" of the data, in which the use of individual drugs or drug classes among women with breast cancer was compared to that among women who had been admitted for other conditions. In addition, we carried out a detailed case-control analysis of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in relation to breast cancer risk. A substantial body of evidence suggests that the use of NSAIDs reduces the risk of colon cancer.[4,5] By contrast, there have been relatively few studies of NSAID use in relation to breast cancer risk and findings have been inconsistent.[6-10] The results of these analyses are described in detail in a manuscript (see Appendix).

In the second year, we assessed the associations seen in the computer screens. In addition, we carried out a detailed case-control analysis of the use of drugs that bind to intracellular histamine receptors in relation to breast cancer risk because there is evidence to suggest that drugs that bind to intracellular histamine receptors may influence the development of breast cancer.[11-15] The results of these analyses are described in detail in a manuscript (Appendix).

BODY

Data. The data used were collected from 1976 through 1996 from patients less than 70 years of age, in hospitals in New York, Philadelphia, Baltimore, and Boston. Nurse-interviewers administered standard questionnaires to obtain information on demographic factors, reproductive and medical history, and habits such as alcohol consumption. Histories of drug use were elicited by questions about 42 indications, such as pain, arthritis, and depression. For each episode of use, the drug name and the duration, timing, and frequency of use were recorded. Details of the diagnoses were abstracted from discharge summaries and pathology reports. Of patients approached, 96% participated.

Computer screen findings

In computer screens, drug use among women who had been diagnosed with breast cancer within the previous year (6957 women) was compared with that of 7262 women who had been admitted for other cancers. For each drug or drug class in turn, odds ratios were computed for use relative to nonuse, with control for age and study center. Over 250 individual drugs and over 150 drug classes (e.g., beta adrenergic blockers, oral anticoagulants) were assessed. Similar

analyses were conducted in which the breast cancer cases were compared with 30,223 women admitted for nonmalignant conditions.

With regard to the screen findings, among drugs which have not previously been assessed in relation to the risk of breast cancer, heparin use and phenytoin use were associated with a statistically significant decreased odds ratio. The odds ratio was increased for clomiphene citrate use.

With respect to heparin, an injectable anticoagulant, there were 67 cases of breast cancer who had used the drug. The association was present whether cancer or noncancer controls were used. The finding was not accounted for by any particular diagnostic category in the controls, nor by age or study center. The odds ratio approximated 0.5 with both cancer and noncancer controls. A review of the literature indicated that there is active investigation in laboratory studies of the possible role of heparin in the etiology of breast cancer.[16-18] For example, it may affect angiogenesis, which is thought to be related to tumor growth.[19] We could find no published epidemiologic findings on the relation of heparin use to breast cancer risk. In the computer screens, oral anticoagulants also were inversely associated with breast cancer risk, but the association was weak and not statistically significant; there is no relevant epidemiologic literature on this topic.

An inverse association of breast cancer risk with phenytoin use (odds ratio 0.5) was present with both cancer and noncancer controls, based on 58 cases of breast cancer who had used phenytoin. The association was not accounted for by any particular diagnostic category in the controls, nor by age or study center. Phenytoin is an anticonvulsant. When we assessed the relation of another class of anticonvulsant drugs to breast cancer risk, barbiturates, we found no association. A literature search did not yield any epidemiologic literature relevant to this topic. There is limited evidence that anticonvulsants such as phenytoin can influence the cytochrome P-450 mono-oxygenase systems,[20] suspected to be involved in the etiology of breast cancer.

The positive association between clomiphene citrate, a fertility drug, and breast cancer risk (odds ratio 1.5) was based on 76 case users, and was present with both cancer and noncancer controls. It was not accounted for by any particular diagnostic group in the controls nor by age or study center. Two small epidemiologic studies provide conflicting evidence on breast cancer: one yielded a small positive association[21] and the other an inverse association.[22] Some experimental evidence suggests that a clomiphene analog has chemopreventive effects against mammary tumors.[23,24] In other possibly relevant epidemiologic data, clomiphene citrate has also been linked to an increased risk of ovarian cancer in a small study.[25]

Insofar as few modifiable risk factors for breast cancer have been identified, the findings from the computer screens may warrant further assessment. If they hold up in detailed analyses similar to those conducted for NSAIDs and drugs that bind to intracellular histamine receptors, assessment in other data bases may be warranted. We note that findings from multiple comparisons, such as the computer screen comparisons, may turn out to be due to chance. The only way to rule out chance as an explanation is to assess the findings in other data.

NSAID use and the risk of breast cancer

The results of this analysis were described in our previous report. A manuscript is included in the Appendix.

Methods. The women included in these analyses were 30 through 69 years of age. The cases comprised 6558 women with a first occurrence of primary breast cancer diagnosed within the previous year, including women with in-situ cancer, who had no concurrent or previous cancer. Two control groups of patients with diagnoses judged to be unrelated to NSAID use were selected. The cancer control group comprised 3296 patients with other malignancies (ovary, uterus, respiratory, nervous system, endocrine); as with the cases, the control cancers had been diagnosed no more than one year previously, and the women had no history of another cancer. The noncancer control group included 2925 patients admitted for trauma or acute infections who had no history of cancer. The controls were frequency-matched to the cases on five-year age group, interview year, and study center.

We defined regular NSAID use as use of an NSAID at least four times per week for three or more months. All other use was considered nonregular. Regular use was further subdivided according to when NSAIDs were first and last used (within the previous year, or at least one year prior to interview). Only use that began a year or more before interview was considered to be etiologically relevant.

Potential confounding was controlled in the analysis: in unconditional logistic regression models used to estimate the odds ratios for regular NSAID use relative to never use, terms were included for age (five-year age group), study center, year of interview (1976-1980, 1981-1985, 1986-1990, 1991-1996), years of education (<12, 12, 13-15, 16+, missing), benign breast disease (yes, no, missing), number of doctor visits two years before hospitalization (0-2, 3-6, 7+, missing), duration of female hormone use (<5 years, 5+years, missing), and duration of oral contraceptive use (0, 1-4 years, 5+ years, missing). A continuous term was used to test for trend across duration of regular NSAID use among users.

Results. The results of the analyses are given in Tables 1-4.

Table 1

NSAID Use in Cases, Cancer Controls, and Noncancer Controls

NSAID use	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1942	1089	1.0	1042	1.0
Nonregular	4086	1873	0.9 (0.8-1.0)	1565	1.0 (0.9-1.1)
Within 1 year of admission only	68	48	0.6 (0.4-1.0)	54	0.5 (0.3-0.8)
Regular use begun ≥1 year before admission	443	269	0.8 (0.7-1.0)	252	0.7 (0.6-0.9)
Discontinued use	109	68	0.7 (0.5-1.0)	54	0.9 (0.7-1.4)
Continuing use	334	201	0.9 (0.7-1.1)	198	0.7 (0.6-0.8)
Unknown	19	17	0.5 (0.2-1.0)	12	0.4 (0.2-1.0)

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 2

Regular NSAID Use that Began ≥1 Year Before Admission, by Duration

Duration	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1942	1089	1.0	1042	1.0
Regular use begun ≥1 year before admission					
<1 year	39	20	0.8 (0.4-1.4)	21	0.9 (0.5-1.7)
1-<2 years	98	51	0.9 (0.7-1.4)	36	1.1 (0.7-1.7)
2-<5 years	125	87	0.7 (0.5-1.0)	75	0.7 (0.5-1.0)
5-<10 years	71	41	0.9 (0.6-1.3)	44	0.7 (0.4-1.0)
10-<20 years	61	37	0.9 (0.6-1.4)	37	0.7 (0.4-1.1)
20+ years	29	18	0.9 (0.5-1.7)	22	0.6 (0.3-1.0)
Unknown	39	32	0.5 (0.3-0.9)	29	0.4 (0.2-0.7)
P for trend			0.98		0.01

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 3

Regular NSAID Use that Began ≥1 Year Before Admission, by Interview Year and Study Center

Subgroup	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
1976-1980	65	58	0.7 (0.4-1.0)	87	0.5 (0.3-0.7)
1981-1985	181	102	0.8 (0.6-1.1)	52	1.0 (0.7-1.5)
1986-1990	76	43	1.4 (0.9-2.2)	48	1.0 (0.6-1.5)
1991-1996	121	66	0.8 (0.6-1.2)	65	0.9 (0.6-1.4)
Boston	28	33	0.5 (0.3-1.0)	81	0.4 (0.2-0.6)
New York	185	67	0.9 (0.6-1.2)	47	1.0 (0.7-1.5)
Philadelphia	200	123	1.0 (0.8-1.3)	110	0.8 (0.6-1.1)
Baltimore	30	46	0.6 (0.3-1.0)	14	1.1 (0.5-2.3)

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 4

NSAID Use in Cases, Cancer Controls, and Noncancer Controls, Excluding Boston

NSAID use	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1743	964	1.0	803	1.0
Nonregular	3716	1580	1.0 (0.9-1.1)	1139	1.0 (0.9-1.2)
Within 1 year of admission only	59	41	0.6 (0.4-1.0)	45	0.4 (0.3-0.7)
Regular use begun ≥1 year before admission	415	236	0.9 (0.7-1.0)	171	0.9 (0.7-1.1)
<1 year	36	17	0.9 (0.5-1.6)	13	1.1 (0.5-2.1)
1-<2 years	93	47	1.0 (0.7-1.4)	24	1.4 (0.9-2.3)
2-<5 years	117	76	0.8 (0.5-1.0)	57	0.7 (0.5-1.0)
5-<10 years	66	35	0.9 (0.6-1.5)	29	0.8 (0.5-1.3)
10-<20 years	57	33	0.9 (0.6-1.5)	26	0.8 (0.5-1.3)
20+ years	28	18	0.9 (0.5-1.7)	15	0.7 (0.4-1.4)
Unknown	35	24	0.6 (0.4-1.1)	14	0.6 (0.3-1.2)
P for trend			0.89		0.06

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Data on nonregular and regular use of NSAIDs among the cases and controls are given in Table 1. For nonregular NSAID use the odds ratio was 0.9 (95% confidence interval (CI) 0.8-1.0) with cancer controls and 1.0 (95% CI 0.9-1.1) with noncancer controls. The odds ratio for use that began in the year before admission was 0.6 (0.4-1.0) using cancer controls and 0.5 (0.3-0.8) using noncancer controls. For subjects who used NSAIDs regularly beginning at least one year before admission, the odds ratio was 0.8 (95% CI 0.7-1.0) using cancer controls, and 0.7 (95% CI 0.6-0.9) using noncancer controls. When we limited the noncancer control group exclusively to subjects admitted for fractures, the odds ratio was 0.9 (95% CI 0.7-1.1). Regular NSAID use that continued into the year before interview (continuing use) was evaluated separately from use that was discontinued one or more years prior to interview (discontinued use). Using cancer controls, the odds ratio was 0.7 (95% CI 0.5-1.0) for discontinued use and 0.9 (95% CI 0.7-1.1) for continuing use. Using noncancer controls, the odds ratio was 0.9 (95% CI 0.7-1.4) for discontinued use and 0.7 (95% CI 0.6-0.8) for continuing use. The results obtained with the cancer controls were unchanged when cancers of the female genital tract (ovary and uterus) were excluded.

Odds ratios according to duration of regular NSAID use are given in Table 2. Using cancer controls, the odds ratio did not decrease as duration of regular use increased (p for trend = 0.98). Using noncancer controls the odds ratio decreased from 0.9 (95% 0.5-1.7) for less than one year of use to 0.6 (95% CI 0.3-1.0) for 20 or more years of use, and the trend was significant (p = 0.01).

As shown in Table 3, the reduction in the odds ratio for regular NSAID use was apparent only in the earliest years of the study (1976 to 1980) (odds ratio (OR) = 0.5, 95% CI 0.3-0.7 using noncancer controls, and 0.7, 95% CI 0.4-1.0 using cancer controls), and in Boston (OR = 0.4, 95% CI 0.2-0.6 using noncancer controls and 0.5, 95% CI 0.3-1.0 using cancer controls). The reduction in risk for regular NSAID use that began at least a year before admission shown in Table 1 was largely accounted for by the reduced risk in the Boston center, which contributed 608 (9%) of the cases. When Boston patients were excluded, the odds ratio for regular NSAID use was 0.9 (95% CI 0.7-1.0) with cancer controls and 0.9 (95% CI 0.7-1.1) with noncancer controls (Table 4). With Boston excluded, the reduction in risk as duration of use increased, using noncancer controls, was attenuated (p for trend = 0.06) (Table 4).

Discussion. In the present data, a small reduction in the odds ratio observed in the overall data for regular NSAID use that began at least a year before admission was largely accounted for by one study center, Boston, that contributed a relatively small amount of data. There was no clear evidence of a risk reduction for quite long durations of use. We can offer no explanation for the findings in Boston other than that the results were based on relatively small numbers and could be due to chance.

In our analysis of colon cancer and NSAID use with data from the Case-Control Surveillance Study,[4] a significant reduction in risk for regular NSAID use that continued into the year before admission (continuing use) was observed, using both cancer controls and noncancer controls, and there was no reduction for discontinued use. In the present analysis of breast cancer, the odds ratio was smaller for discontinued use than for recent use when cancer controls

were used, whereas the opposite was the case with noncancer controls. The inconsistencies in the present findings weaken support for a protective effect of NSAID use against breast cancer.

Limited data from animal studies[26-30] have suggested a protective effect of NSAIDs against mammary cancer. Previous results from epidemiologic studies of NSAID use and breast cancer have been equivocal. Two case-control studies, one population based[7] and one hospital based[6] estimated reductions in risk on the order of 30 to 40%. In the hospital based study, the results varied according to whether cancer or noncancer controls were used: the odds ratio was significantly reduced, 0.6, using noncancer controls, but there was no reduction using cancer controls. A 30% reduction in risk was found among women in the NHANES I cohort who reported taking any aspirin in the month prior to commencement of follow-up.[8] The imprecise definition of aspirin use, lack of information on dose or duration, and the fact that the risk reduction for breast cancer was bigger than that reported in the same data for colorectal cancer renders these results unconvincing. Two other cohort studies found no association between aspirin use and breast cancer risk. The large Nurses' Health Study found that the use of two or more aspirins per week was unrelated to breast cancer incidence over 12 years of follow-up.[9] In a cohort of elderly persons, the relative risk for daily aspirin use at entry was 0.96.[10] There was no information on aspirin use after entry, and follow-up was less than seven years.

Based on the present results and other studies, it seems safe to conclude that NSAID use does not increase the risk of breast cancer. If there is a protective effect, it is likely to be quite small and perhaps beyond the resolving powers of observational methods.

Use of drugs that bind to intracellular histamine receptors in relation to the risk of breast cancer

The results of this analysis are described in detail in a manuscript included in the Appendix.

Introduction. In experimental studies in rodents, some antidepressants and structurally similar compounds, such as antihistamines, have been shown to increase the growth of mammary tumors. It has been suggested that these drugs promote growth by binding to anti-estrogen binding site/intracellular histamine receptors.[11-15] An association between depression and the occurrence of cancer has been observed in some epidemiologic studies,[31,32] but others have observed no association.[33-37] Only two studies have assessed the use of antidepressants in relation to risk of breast cancer and the results have been conflicting.[38,39] In recent years, a new class of antidepressants, the selective seratonin reuptake inhibitors (SSRIs) have become widely used. Their relationship to risk of breast cancer has not been assessed. In the present analysis, we undertook to assess the relation of use of drugs that bind to intracellular histamine receptors--SSRIs, tricylcic antidepressants, other antidepressants, phenothiazines, and antihistamines--to the risk of breast cancer.

The women included in the present analyses were under 70 years of age, interviewed during 1977-1996 in collaborating hospitals in Boston, New York, Baltimore, and Philadelphia. The cases comprised 5814 with primary breast cancer diagnosed within the previous year, not

including women with in-situ cancer; women who had a history of prior cancer were excluded. Two groups of patients with diagnoses judged to be unrelated to the use of any of the study drugs were selected. The cancer control group consisted of 5095 women who no history of previous cancer who had been diagnosed within the last year with cancer of the gastrointestinal system, bone, connective tissue, skin, or other sites. A control group of women with nonmalignant conditions was selected from among 19955 women who had no history of cancer and who had been admitted for trauma, gastrointestinal disorders, acute infections, or a variety of other conditions. They were selected at random to attain frequency matching to the cases on decade of age, region, and date of interview. Thus, the final noncancer control group consisted of 5814 women.

We defined regular use of any of the antidepressants, antihistamines, or phenothiazines as use for at least four days per week for at least a month. Regular use was subdivided according to whether it had begun within the year before admission or at least a year before admission; the former category was not etiologically relevant.

Relative risk estimates (odds ratios) were estimated from unconditional logistic regression analyses which included indicator terms for age, region, race, religion, year of interview, age at first birth, body mass index, history of cystic breast disease, alcohol consumption, and number of previous hospitalizations.

Results. The results of the analyses are given in Tables 5-8.

Table 5

Use of Antidepressants, Phenothiazines, and Antihistamines Among
5814 Women with Breast Cancer, 5095 Cancer Controls, and 5814 Noncancer Controls

Drug	Cases	Cancer controls		Noncancer controls	
		No.	Multivariate relative risk* (95% confidence interval)	No.	Multivariate relative risk* (95% confidence interval)
Tricyclic antidepressants					
Regular†	142	100	1.1 (0.8-1.5)	171	0.8 (0.6-1.0)
Other	62	42	1.0 (0.7-1.6)	55	1.0 (0.7-1.5)
First use <12 months	29	44	0.5 (0.3-0.8)	39	0.7 (0.4-1.2)
SSRI antidepressants					
Regular†	28	15	1.6 (0.8-3.2)	19	1.5 (0.8-2.8)
Other	3	1	---	1	---
First use <12 months	11	19	0.5 (0.2-1.1)	12	1.1 (0.5-2.6)
Other antidepressants					
Regular†	26	18	1.1 (0.6-2.0)	23	1.0 (0.6-1.9)
Other	21	12	1.6 (0.8-3.5)	13	1.7 (0.8-3.5)
First use <12 months	2	4	---	5	---
Phenothiazines					
Regular†	91	57	1.3 (0.9-1.9)	108	0.9 (0.6-1.1)
Other	83	68	0.8 (0.6-1.2)	92	0.7 (0.5-1.0)
First use <12 months	84	94	0.9 (0.7-1.3)	16	6.9 (3.9-12)
Antihistamines					
Regular†	147	131	0.9 (0.7-1.2)	164	0.8 (0.6-1.0)
Other	1590	1055	1.0 (0.9-1.1)	1323	1.1 (1.0-1.2)
First use <12 months	92	95	0.8 (0.6-1.2)	111	0.9 (0.7-1.3)

*Reference category is never use of each drug group.

†Use at least 4 days/week for at least 4 weeks, excluding use begun ≤1 year before admission.

Table 6 (1 of 2)

Individual Drugs* Taken Regularly by 5814 Cases and 10909 Controls

Drug group Drug	Cases	Controls	Multivariate relative risk (95% confidence interval)
Tricyclic antidepressants			
Amitriptyline	88	209	0.8 (0.6-1.1)
Imipramine	33	52	1.1 (0.7-1.7)
Doxepin	14	23	1.2 (0.6-2.5)
Desipramine	6	10	---
Nortriptyline	4	11	---
Protriptyline	1	0	---
Clomipramine	1	1	---
Amoxapine	2	1	---
Trimipramine	0	1	---
SSRI antidepressants			
Fluoxetine	23	27	1.5 (0.8-2.6)
Sertraline	4	4	---
Paroxetine	2	4	---
Other antidepressants			
Trazodone	4	9	---
Maprotiline	1	2	---
Bupropion	1	1	---
Venlafaxine	0	1	---
Antidepressant/Mood elevator, NOS	20	28	---
Phenothiazines			
Perphenazine	28	54	1.0 (0.6-1.6)
Trifluoperazine	20	26	1.4 (0.8-2.6)
Prochlorperazine	15	39	0.6 (0.3-1.2)
Chlorpromazine	22	30	1.4 (0.8-2.6)
Thioridazine	20	29	1.2 (0.6-2.1)
Fluphenazine	2	3	---
Mesoridazine	1	1	---
Promazine	1	0	---
Ethopropazine	0	2	---

*Subjects may have taken >1 drug in each group.

Table 6 (2 of 2)

Individual Drugs* Taken Regularly by 5814 Cases and 10909 Controls

Drug group Drug	Cases	Controls	Multivariate relative risk (95% confidence interval)
Antihistamines			
Chlorpheniramine	50	87	0.9 (0.6-1.3)
Doxylamine	23	42	0.9 (0.5-1.6)
Triprolidine	13	25	0.9 (0.5-1.9)
Brompheniramine	16	22	1.3 (0.6-2.5)
Terfenadine	13	26	0.8 (0.4-1.7)
Hydroxyzine	10	30	0.7 (0.3-1.4)
Diphenhydramine	9	41	---
Pyrilamine	8	14	---
Phenyltoxamine	5	10	---
Cyproheptadine	5	2	---
Dexbrompheniramine	4	14	---
Methapyrilene	4	12	---
Astemizole	4	6	---
Clemastine	4	2	---
Dimethindene	3	8	---
Dexchlorpheniramine	3	5	---
Antazoline	3	4	---
Promethazine	3	4	---
Pyrrobutamine	2	4	---
Carbinoxamine	2	2	---
Pheniramine	1	3	---
Dimenhydrinate	1	2	---
Tripelennamine	1	2	---
Thenyldiamine	1	1	---
Loratadine	0	2	---
Trimethobenzamide	0	2	---
Pyribenzamine	0	1	---
Trimeprazine	0	1	---
Antihistamine, NOS	5	9	---

*Subjects may have taken >1 drug in each group.

Table 7

Risk of Breast Cancer According to Duration of Regular Use of Antidepressants, Phenothiazines, and Antihistamines Among 5814 Breast Cancer Cases and 10909 Controls

Drug Duration (years)	Cases	Controls	Multivariate relative risk* (95% confidence interval)
Tricyclic antidepressants			
<1	36	81	0.7 (0.4-1.0)
1-4	76	111	1.3 (0.9-1.8)
5-9	11	44	0.5 (0.2-0.9)
≥10	19	35	1.0 (0.5-1.8)
SSRI antidepressants			
<1	5	9	1.3 (0.4-4.0)
1-2	16	15	2.1 (1.0-4.4)
≥3	7	9	1.3 (0.4-3.6)
Other antidepressants			
<1	10	19	0.8 (0.4-1.8)
1-4	11	14	1.2 (0.5-2.8)
≥5	5	8	1.3 (0.4-4.1)
Phenothiazines			
<1	23	53	0.6 (0.4-1.1)
1-4	36	54	1.2 (0.8-1.9)
5-9	15	23	1.3 (0.6-2.5)
≥10	17	35	1.2 (0.6-2.1)
Antihistamines			
<1	29	50	1.0 (0.6-1.6)
1-4	49	92	0.9 (0.7-1.4)
5-9	24	38	1.1 (0.7-1.9)
≥10	45	115	0.6 (0.4-0.9)

*Reference category is never use of particular drug.

Table 8

Risk of Breast Cancer According to Interval Since Last Regular Use of Antidepressants, Phenothiazines, and Antihistamines Among 5814 Breast Cancer Cases and 10909 Controls

Drug Interval since last use (years)	Cases	Controls	Multivariate relative risk* (95% confidence interval)
Tricyclic antidepressants			
<1	66	127	1.0 (0.7-1.4)
1-4	21	67	0.5 (0.3-0.9)
5-9	17	35	0.6 (0.3-1.2)
≥10	30	34	1.4 (0.8-2.4)
SSRI antidepressants			
<1	22	23	1.8 (1.0-3.4)
≥1	6	11	1.1 (0.4-3.1)
Other antidepressants			
<1	11	17	1.1 (0.5-2.4)
1-4	8	10	1.3 (0.5-3.4)
≥5	7	13	0.8 (0.3-2.3)
Phenothiazines			
<1	44	70	1.3 (0.9-2.0)
1-4	8	25	0.5 (0.2-1.2)
5-9	17	19	1.5 (0.8-3.1)
≥10	21	47	0.7 (0.4-1.3)
Antihistamines			
<1	93	182	0.9 (0.7-1.2)
1-4	21	42	0.8 (0.4-1.3)
5-9	8	18	0.8 (0.3-1.9)
≥10	18	30	1.0 (0.6-1.9)

*Reference category is never use of particular drug.

As shown in Table 5, for each of the five classes of drugs considered--tricyclic antidepressants, SSRI antidepressants, other antidepressants, phenothiazines, and antihistamines--the relative risk estimates for regular use were compatible with 1.0 whether cancer or noncancer controls were used. The estimates for regular use of SSRIs were somewhat elevated--1.6. with cancer controls and 1.5. with noncancer controls--but neither estimate was statistically significant. Nonregular use of the five drug categories was not significantly associated with breast cancer risk. With respect to drug use that was initiated in the year before admission, there was a statistically significant elevation in relative risk, 6.9, estimated with noncancer controls for phenothiazine use; this association was probably accounted for by the use of phenothiazines for nausea associated with chemotherapy for breast cancer.

Table 6 gives relative risk estimates for regular use of individual drugs within the five drug classes considered; in these analyses the cancer and noncancer control groups were combined. Amitriptyline was the most commonly used tricyclic antidepressant. The relative risk estimates for amitriptyline and for the other individual tricyclic antidepressants considered were compatible with 1.0. Fluoxetine (Prozac) was the most commonly used SSRI. The relative risk estimate, 1.5, was compatible with a value of 1.0. Among the phenothiazines, five individual drugs were commonly enough used to assess separately: the relative risk estimates ranged from 0.6 to 1.4 and were compatible with 1.0. Six individual antihistamines were assessed: the relative risk estimates ranged from 0.7 to 1.3 and none was statistically significant.

Table 7 gives data on the five drug classes according to the total duration of regular use. There was no evidence of a trend of increasing or decreasing relative risk with increasing duration of use. For SSRI antidepressants, the relative risk estimate for 1-2 years of use was elevated, 2.1 (95% CI 1.0-4.4), but the estimate for 3 or more years of use was 1.3.

Table 8 gives data on the interval since last use of each of the five classes of drugs. If these drugs act as "promoters", one might expect to find an increased risk for recent use. The estimate for use that continued into the year before admission for SSRIs was 1.8 (95% CI 1.0-3.4). For tricyclic antidepressants, other antidepressants, phenothiazines, and antihistamines, the corresponding relative risk estimates ranged from 0.9 to 1.3 and were compatible with 1.0 If these drugs act as "initiators", use in the distant past might be associated with an increased risk. Relative risk estimates for use that ended at least 10 years previously were compatible with 1.0 for tricyclic antidepressants, other antidepressants, phenothiazines, and antihistamines. There was no SSRI use in the distant past, because these drugs have only been used in recent years.

Discussion. The results of the present study were null for tricyclic antidepressants, other antidepressants other than SSRIs, phenothiazines, and antihistamines. There was no evidence to suggest that long-term use, recent use, or use in the distant past increased the risk. For SSRIs, the relative risk estimate was increased for recent use, 1.8, but the 95% CI included 1.0; there was no clear evidence of increasing risk with increasing duration of use.

The present results provide little support for the hypothesis that drugs that bind to intracellular histamine receptors influence breast cancer risk. However, while largely null, the results are not entirely reassuring with regard to SSRIs. SSRIs are now among the most widely

used prescription drugs in the United States and for that reason alone, it is important to continue to monitor their relation to the risk of breast cancer.

CONCLUSIONS

Computer screens

Inverse associations with heparin use and phenytoin use were observed. The role of heparin in the etiology of breast cancer is under active investigation in laboratory experiments. We could find no relevant epidemiologic literature on the relation to breast cancer risk to either of these drugs.. A weak positive association with clomiphene citrate use was also observed. The epidemiologic literature on this topic is sparse and inconsistent. Few modifiable risk factors for breast cancer have been identified. These associations with relatively commonly used medications may warrant detailed investigation in the present database, similar to the analyses carried out for NSAIDs and drugs that bind to intracellular histamine receptors. If the associations hold up after detailed assessment of potential confounders, assessment in further data might be warranted.

NSAID use and the risk of breast cancer

Our results suggest that NSAID use does not increase the risk of breast cancer. The results are compatible with no association or even a small decrease in risk. However, if there is a decrease in risk, it is smaller than that observed for large bowel cancer and its establishment may be beyond the resolving power of epidemiologic studies.

Use of drugs that bind to intracellular histamine receptors in relation to the risk of breast cancer

Our assessment of four classes of drugs that bind to intracellular histamine receptors--tricyclic antidepressants, other antidepressants, phenothiazines, and antihistamines--yielded null results. However, the results for SSRIs were not entirely reassuring. There was no evidence of an increase in risk with increasing duration of use, but the relative risk estimate for recent use was elevated, 1.8 (95% CI 1.0-3.4). That estimate was based on relatively small numbers: 22 case users and 23 control users. SSRIs are now among the most commonly prescribed prescription drugs in the United States. For that reason alone, their relation to the risk of breast cancer warrants monitoring in the future.

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APPENDIX

"The relationship of nonsteroidal anti-inflammatory drug use to the risk of breast cancer"

"Risk of breast cancer according to use of antidepressants, phenothiazines, and antihistamines"

THE RELATIONSHIP OF NONSTEROIDAL ANTI-INFLAMMATORY DRUG USE TO THE RISK OF BREAST CANCER

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Abstract

Background. The effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of breast cancer is unclear. We assessed the association in a hospital-based case control study.

Methods. The cases (n=6558) were compared with cancer controls (n=3296) and noncancer controls admitted for trauma or acute infection (n=2925). Odds ratios were estimated using multivariate logistic regression models.

Results. For women who used NSAIDs regularly beginning at least one year before admission, the odds ratio (OR) was 0.8 (95% confidence interval (CI) 0.7,1.0) with cancer controls, and 0.7 (95% CI 0.6,0.9) with noncancer controls. With noncancer controls, there was a statistically significant decreasing trend in the odds ratios as duration of use increased, whereas with cancer controls there was not. The reduction in risk for regular use was accounted for largely by a reduced odds ratio for one study center (Boston), which contributed 9% of the cases. When Boston subjects were excluded, the OR for regular NSAID use was 0.9 (95% CI 0.7,1.0) with cancer controls and 0.9 (95% CI 0.7,1.1) with noncancer controls, and the trend with noncancer controls was attenuated.

Conclusions. Due to inconsistencies in the data, the present findings offer little support for a protective effect of NSAIDs against breast cancer.

KEY WORDS: breast cancer, epidemiology, pharmacoepidemiology, environmental factors

Précis: In this hospital-based case control study, we observed a slight reduction in breast cancer risk for women who used NSAIDs regularly, compared to never-users, but inconsistencies in the data detract from a causal interpretation.

INTRODUCTION

A growing body of epidemiological evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the risk of colon cancer (1-5). By contrast, findings on the relation of NSAID use to breast cancer risk have been inconsistent. Two case-control studies reported reductions in breast cancer risk of 30% to 40% (6,7), and there was a similar 30% risk reduction among women in the NHANES I cohort who reported taking aspirin in the month before the commencement of follow-up (8). Other studies have not shown an inverse association of NSAID use with breast cancer risk (9,10). A protective effect of NSAID use on breast cancer risk could have important public health implications, as it would be one of the only modifiable preventives for the disease yet identified.

We have used data from the multipurpose hospital-based Case Control Surveillance Study to evaluate the association between regular NSAID use and breast cancer risk. This surveillance study was designed to detect effects of prescription and over-the-counter medications on the risk of various cancers. The study includes over 6500 cases of breast cancer and adequate numbers of appropriate controls, with detailed information on duration, timing, and frequency of use of aspirin as well as non-aspirin NSAIDs. Thus it is one of the most informative bodies of data on the breast cancer-NSAID relationship assembled to date.

METHODS

Data Collection

The data were collected from 1976 through 1996 from patients in hospitals in New York, Philadelphia, Baltimore, and Boston. Nurse-interviewers administered standard questionnaires to obtain information on demographic factors, reproductive and medical history, and habits such as

alcohol consumption. Histories of drug use were elicited by questions about 42 indications, which included those for which NSAIDs are used (e.g., pain, headache, and arthritis). For each episode of use, the drug name and the duration, timing, and frequency of use were recorded. Details of the diagnoses were abstracted from discharge summaries and pathology reports. The present analyses are based on female patients aged 30 through 69 years. Ninety-six percent of patients approached for an interview participated. Approval to interview study subjects was obtained from the Institutional Review Boards of all participating institutions.

Cases

The cases comprised 6558 women with a first occurrence of primary breast cancer diagnosed within the previous year, confirmed by pathology report, and no concurrent or previous cancer.

Controls

Two control groups of patients with diagnoses judged to be unrelated to NSAID use were selected. A cancer control group comprised 3296 patients with ovarian or uterine cancer (49%), malignant melanoma (21%), respiratory system cancers (22%), and nervous system or endocrine cancers (8%). None of these cancers have been associated with NSAID use. As with the cases, the control cancers had been diagnosed no more than one year previously, and there was also no history of another cancer. A noncancer control group included 2925 patients admitted for trauma (56%) or acute infection (44%), who had no history of cancer. The controls were frequency-matched to the cases on five-year age group, interview year, and study center.

Analysis

NSAID use was defined as use of any drug in the following classes: salicylates (e.g., aspirin), indoles (e.g., indomethacin), propionic acids (e.g., ibuprofen), fenamates (e.g., mefenamic acid), pyrazolines (e.g., phenylbutazone), and oxicams (e.g., piroxicam). Most use was sporadic. We judged that if NSAID use has a preventive role, it would most likely be regular use of long duration. We defined regular NSAID use to be use of any NSAID at least four times per week for three or more months. All other use was considered nonregular. Regular use was further subdivided according to when NSAIDs were first and last used (within the previous year, or more than one year prior to admission). Only use that began a year or more before admission was considered to be etiologically relevant.

The prevalence of regular NSAID use that began at least one year before admission, adjusted for study center and five-year age group, was 7.3% among cancer controls and 9.2% among noncancer controls. The prevalence varied by year of interview (higher in later years), geographic area (highest in Philadelphia and lowest in New York), and age (higher at older ages). Use was also positively associated with years of education, benign breast disease, number of doctor visits two years prior to hospitalization, and use of hormone supplements and oral contraceptives. Potential confounding by all these factors was controlled in the analysis.

Unconditional logistic regression models were used to estimate the odds ratios for regular NSAID use relative to never use (no use at all) with control for age (five-year age group), study center, year of interview (1976-1980, 1981-1985, 1986-1990, 1991-1996), years of education (<12, 12, 13-15, 16+, missing), benign breast disease (yes, no, missing), number of doctor visits two years before hospitalization (0-2, 3-6, 7+, missing), duration of female hormone use (<5 years, 5+years, missing), and duration of oral contraceptive use (0, 1-4 years, 5+ years, missing).

We also included the following variables in the model: age at menarche, age at menopause, age at first birth, parity, race, alcohol consumption, religion, breast cancer in mother or sister, practice of breast self examination, and body mass index. Although their relation with breast cancer risk was of the expected direction and magnitude, these variables did not alter the effect of NSAID use, hence they were excluded from the final model. A continuous term was used to test for trend across duration of regular NSAID use among users.

RESULTS

Data on nonregular and regular use of NSAIDs among cases and controls are given in Table 1. For nonregular NSAID use the odds ratio was 0.9 (95% confidence interval (CI) 0.8,1.0) with cancer controls and 1.0 (95% CI 0.9,1.1) with noncancer controls. The odds ratio for regular use that began in the year before admission was 0.6 (0.4-1.0) with cancer controls and 0.5 (0.3-0.8) with noncancer controls. For subjects who used NSAIDS regularly beginning at least one year before admission, the odds ratio was 0.8 (95% CI 0.7,1.0) with cancer controls, and 0.7 (95% CI 0.6,0.9) with noncancer controls (Table 1). When we limited the control group exclusively to subjects admitted for fractures, the odds ratio was 0.9 (95% CI 0.7,1.1). Regular NSAID use that continued into the year before admission (continuing use) was evaluated separately from use that was discontinued one or more years prior to admission (discontinued use). With cancer controls, the odds ratio was 0.7 (95% CI 0.5,1.0) for discontinued use and 0.9 (95% CI 0.7,1.1) for continuing use. With noncancer controls, the odds ratio was 0.9 (95% CI 0.7,1.4) for discontinued use and 0.7 (95% CI 0.6,0.8) for continuing use. The results obtained with the cancer controls were unchanged when cancers of the female genital tract (ovary and

uterus) were excluded (data not shown). All further analyses are confined to regular use that was initiated at least a year prior to admission.

We considered the effect of aspirin (the most commonly used NSAID) and non-aspirin NSAIDs separately. The odds ratio for regular aspirin use, compared to no NSAID use, was 0.7 (95% CI 0.6,0.9) with cancer controls and 0.7 (95% CI 0.5,0.8) with noncancer controls. The odds ratio for non-aspirin NSAID use was 0.9 (95% CI 0.7,1.2) with cancer and 0.8 (95% CI 0.6,1.1) with noncancer controls.

Odds ratios according to duration of regular NSAID use are given in Table 2. With cancer controls, the odds ratio did not decrease as duration of regular use increased (p for trend=0.98). With noncancer controls the odds ratio decreased from 0.9 (95% CI 0.5,1.7) for less than one year's use to 0.6 (95% CI 0.3,1.0) for more than 20 years use, and the trend was significant (p=0.01).

The reduction in the odds ratio for regular NSAID use was apparent only in the earliest years of the study (1976 to 1980) (OR=0.5, 95% CI 0.3,0.7 with noncancer controls, and 0.7, 95% CI 0.4,1.0 with cancer controls), and in Boston (OR=0.4, 95% CI 0.2,0.6 with noncancer controls and 0.5, 95% CI 0.3,1.0 with cancer controls) (Table 3). The overall reductions in risk seen with both cancer and noncancer controls (Table 1) are largely accounted for by the reduced risk in the Boston center, which contributed only 608 (9%) of the cases. When Boston patients were excluded, the odds ratio for regular NSAID use was 0.9 (95% CI 0.7,1.0) with cancer controls and 0.9 (95% CI 0.7,1.1) with noncancer controls (Table 4). With Boston excluded, the reduction in risk as duration of use increased, with noncancer controls, is attenuated (p for trend=0.06) (Table 4). In addition, with Boston excluded, the odds ratio for aspirin use is 0.8

(95% CI 0.6,1.0) and 0.8 (0.6,1.1) with cancer and noncancer controls, respectively (data not shown).

DISCUSSION

An observed 30% decrease in breast cancer risk among regular NSAID users, with cancer controls, was unconvincing due to inconsistencies in the data. The risk reduction was observed only when noncancer controls were used, and was accounted for by one study center, Boston, that contributed a relatively small amount of data. With Boston excluded, the odds ratios for regular use begun at least one year before admission approached the null, whether cancer or noncancer controls were used. A decreasing trend in risk as duration of regular use increased was observed again only when noncancer controls were used, and the trend was weakened when the Boston center was excluded. We can offer no explanation for the findings in Boston other than the results were based on relatively small numbers (28 exposed cases) and could be due to chance.

A protective effect was also only apparent during the earlier years of the study, probably because 60% of the Boston cases were interviewed during these years. We are not aware of any changes in hospital admission policies for trauma or acute infection after the initial study period which could account for the difference in results by time period. A true protective effect of NSAIDS on breast cancer risk should be consistent across study centers, years, and control groups.

With regard to the noncancer controls, we judged that trauma and acute infections were diagnoses which were not related to NSAID use and for which hospital admission was largely obligatory. However, when we limited the noncancer controls to one group for whom admission was absolutely obligatory - fractures - the odds ratio approached the null. Thus NSAID users

may have been slightly overrepresented in the total noncancer control group. Overall, however, we believe any selection bias in the study was not major, because there was no risk reduction for nonregular NSAID use with either cancer or noncancer controls.

In our analysis of colon cancer and NSAID use in these same data (1), a significant reduction in risk for regular NSAID use that continued into the year before admission (continuing use) was observed, with both cancer controls (OR=0.6, 95% CI 0.4,0.9) and controls admitted for trauma and infection (OR=0.5, 95% CI 0.4,0.8), and there was no reduction for discontinued use. In the present analysis of breast cancer, the odds ratio was smaller for discontinued use than for recent use when cancer controls were used, whereas the opposite was the case with noncancer controls. Compared to the consistent evidence of a major protective effect of NSAID use against colon cancer, the inconsistent evidence for a modest protective effect against breast cancer is not persuasive.

Several potential confounding factors were controlled in the analyses. However, estimates adjusted only for age and study center (data not shown) differed little from the adjusted results presented here. A long list of other breast cancer risk factors had no effect on the odds ratios, and were not included in the final model. Therefore, we believe that our results are relatively unconfounded. It is also unlikely that recall bias affected these results since at the time data were collected, the study hypothesis was unknown to investigators, interviewers, and subjects.

NSAIDs inhibit the synthesis of prostaglandins through interference with the arachidonic acid cascade. Subsequent effects on immune function or apoptosis are the likely mechanisms by which NSAIDs protect against colon cancer. Prostaglandins may be particularly important to colon carcinogenesis since colon tumors produce large amounts of prostaglandins, and there is a

positive correlation between tumor size and prostaglandin output (5). It is not clear whether a prostaglandin-based mechanism is relevant to breast carcinogenesis, although a limited number of animal studies (11-15) have suggested a protective effect of NSAIDs against mammary cancer. In one rat study (15), a sulfone metabolite of sulindac inhibited mammary carcinogenesis apparently through an effect that did not involve prostaglandins.

Previous results from epidemiologic studies of NSAID use and breast cancer have been equivocal. Two case control studies, one population based (7) and one hospital based (6) estimated reductions in risk on the order of 30 to 40%. In the hospital based study, the magnitude of the risk reduction varied according to whether cancer or noncancer controls were used: the odds ratio with noncancer controls was 0.6 (95% CI 0.4,0.8) for use of NSAIDs at least three times per week for at least five years, compared to 1.05 (95% CI 0.6,2.0) with cancer controls. These results may be explained by a higher prevalence of preexisting medical conditions commonly associated with NSAID use among the noncancer controls. The population-based studies used as controls subjects who underwent screening mammography, and their use of NSAIDs could have overestimated the prevalence of use in the study base (7).

A 30% reduction in risk (95% CI 4%,50%) was found among women in the NHANES I cohort who reported taking any aspirin in the month prior to commencement of follow-up (8). The imprecise definition of aspirin use, lack of information on frequency or duration of use, and the fact that the risk reduction for breast is larger than that reported in the same data for colorectal cancer (OR=0.9, 95% CI 0.6,1.2) renders these results unconvincing. Two other cohort studies found no association between aspirin use and breast cancer risk. In the large Nurses' Health Study, the use of two or more aspirins per week was unrelated to breast cancer incidence over 12 years of follow-up (9). In a cohort of elderly persons followed for incident

cancers for seven years, the relative risk for daily aspirin use at entry was 0.96 (10). This study was based on 35 exposed cases, and was adjusted only for age.

We conclude that the present findings, from a very large study designed specifically to evaluate medications and cancer, offer little support for a protective effect of NSAIDs against breast cancer. Previous studies also fail to provide consistent evidence of a protective effect. It seems safe to conclude that NSAID use does not increase the risk of breast cancer. In addition, if there is a protective effect, it is likely to be quite small and perhaps beyond the resolving powers of observational methods.

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Table 1

NSAID Use in Cases, Cancer Controls, and Noncancer Controls

NSAID use	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1942	1089	1.0	1042	1.0
Nonregular	4086	1873	0.9 (0.8,1.0)	1565	1.0 (0.9,1.1)
Regular use within 1 year of admission only	68	48	0.6 (0.4,1.0)	54	0.5 (0.3,0.8)
Regular use begun ≥1 year before admission	443	269	0.8 (0.7,1.0)	252	0.7 (0.6,0.9)
Discontinued use	109	68	0.7 (0.5,1.0)	54	0.9 (0.7,1.4)
Continuing use	334	201	0.9 (0.7,1.1)	198	0.7 (0.6,0.8)
Unknown	19	17	0.5 (0.2,1.0)	12	0.4 (0.2,1.0)

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 2

Regular NSAID Use that Began ≥1 Year Before Admission, by Duration

Duration	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1942	1089	1.0	1042	1.0
Regular use begun ≥1 year before admission					
<1 year	39	20	0.8 (0.4,1.4)	21	0.9 (0.5,1.7)
1-<2 years	98	51	0.9 (0.7,1.4)	36	1.1 (0.7,1.7)
2-<5 years	125	87	0.7 (0.5,1.0)	75	0.7 (0.5,1.0)
5-<10 years	71	41	0.9 (0.6,1.3)	44	0.7 (0.4,1.0)
10-<20 years	61	37	0.9 (0.6,1.4)	37	0.7 (0.4,1.1)
20+ years	29	18	0.9 (0.5-1.7)	22	0.6 (0.3,1.0)
Unknown	39	32	0.5 (0.3,0.9)	29	0.4 (0.2,0.7)
P for trend			0.98		0.01

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 3

Regular NSAID Use that Began ≥1 Year Before Admission, by Interview Year and Study Center

Subgroup	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
1976-1980	65	58	0.7 (0.4,1.0)	87	0.5 (0.3,0.7)
1981-1985	181	102	0.8 (0.6,1.1)	52	1.0 (0.7,1.5)
1986-1990	76	43	1.4 (0.9,2.2)	48	1.0 (0.6,1.5)
1991-1996	121	66	0.8 (0.6,1.2)	65	0.9 (0.6,1.4)
Boston	28	33	0.5 (0.3,1.0)	81	0.4 (0.2,0.6)
New York	185	67	0.9 (0.6,1.2)	47	1.0 (0.7,1.5)
Philadelphia	200	123	1.0 (0.8,1.3)	110	0.8 (0.6,1.1)
Baltimore	30	46	0.6 (0.3,1.0)	14	1.1 (0.5,2.3)

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Table 4

NSAID Use in Cases, Cancer Controls, and Noncancer Controls, Excluding Boston

NSAID use	Cases	Cancer controls	OR* (95% CI)	Noncancer controls	OR* (95% CI)
Never	1743	964	1.0	803	1.0
Nonregular	3716	1580	1.0 (0.9,1.1)	1139	1.0 (0.9,1.2)
Regular use within 1 year of admission only	59	41	0.6 (0.4,1.0)	45	0.4 (0.3,0.7)
Regular use begun ≥1 year before admission	415	236	0.9 (0.7,1.0)	171	0.9 (0.7,1.1)
<1 year	36	17	0.9 (0.5,1.6)	13	1.1 (0.5,2.1)
1-<2 years	93	47	1.0 (0.7,1.4)	24	1.4 (0.9,2.3)
2-<5 years	117	76	0.8 (0.5,1.0)	57	0.7 (0.5,1.0)
5-<10 years	66	35	0.9 (0.6,1.5)	29	0.8 (0.5,1.3)
10-<20 years	57	33	0.9 (0.6,1.5)	26	0.8 (0.5,1.3)
20+ years	28	18	0.9 (0.5,1.7)	15	0.7 (0.4,1.4)
Unknown	35	24	0.6 (0.4,1.1)	14	0.6 (0.3,1.2)
P for trend			0.89		0.06

*Adjusted for age, study center, interview year, years of education, history of benign breast disease, number of doctor visits two years before admission, duration of use of oral contraceptives, duration of use of female hormone supplements.

Risk of Breast Cancer According to Use of Antidepressants, Phenothiazines, and Antihistamines

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ABSTRACT

Background. In laboratory studies, some antidepressants and structurally similar antihistamines have been shown to increase the growth of mammary tumors. The relation of use of these drugs to the development of breast cancer was examined in a case-control study.

Methods. Information, including a lifetime medication history, was collected by interview from 5814 women hospitalized with primary breast cancer diagnosed within the previous year, and women hospitalized for other conditions, including 5095 with primary malignancies of sites other than the breast and reproductive system, and 5814 women with nonmalignant conditions. Relative risks (RR) were estimated using unconditional multiple logistic regression for regular use ($\geq$4 days per week for $\geq$4 weeks, beginning $\geq$1 year before admission) of several classes of antidepressants (selective serotonin reuptake inhibitors [SSRI], tricyclics, and others), phenothiazines, and antihistamines.

Results. With reference to never use of each drug, RR estimates for regular use were statistically compatible with 1.0 for SSRIs, tricyclics, other antidepressants, phenothiazines, and antihistamines; results were closely similar using the cancer or noncancer controls. There were no statistically significant increases in relative risk for any category when regular use was stratified according to cumulative duration of use, or time interval since last use. However, the RR estimate for regular use of SSRIs in the previous year, 1.8, was of borderline statistical significance (95% confidence interval 1.0-3.4).

Discussion. The findings do not support an association between use of tricyclic antidepressants, antidepressants other than SSRIs, phenothiazines, or antihistamines and the development of breast cancer. The results for SSRIs, however, were not entirely reassuring. The

frequency with which both the outcome and the exposures occur warrant the evaluation of these relationships in other human studies.

INTRODUCTION

Experimental studies in mice and rats have demonstrated accelerated growth of mammary tumors in animals exposed to some antidepressants.[1,2] The authors of these studies suggest that amitriptyline and fluoxetine act as promoters of malignant growth in the presence of a carcinogen, by binding to anti-estrogen binding site/intracellular histamine receptors (H_{1C}).[3,4] These drugs are structurally similar to the prototype compound DPPE which binds to the same receptors which are present in cell microsomes and nuclei and play a role in growth regulation. Other drugs which resemble the structure of DPPE are the arylalkylamine antihistamines and phenothiazines; laboratory studies have demonstrated that these drugs bind to this site and increase the growth of mammary tumors.[5] Thus, there is some mechanistic basis for an association between depression and the occurrence of cancer observed in some epidemiologic studies.[6-7] However other studies[8-12] have reported no association of depression with cancer, and only two studies, one positive and one negative,[13,14] have investigated the use of antidepressant drugs in humans as a risk factor for breast cancer.

Amitriptyline (marketed as Elavil, Adepril, Saroten, etc.), is a tricyclic antidepressant, while fluoxetine (Prozac) belongs to the relatively new class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs). Because of their efficacy and a favorable side-effect profile, the latter drugs have become widely used in the last decade, and are among the most frequently prescribed drugs in the United States. If these, or structurally similar drugs, influence the development or growth of breast cancer, this would have important public health implications.

We examined the relation of exposure to antidepressants, antihistamines, and phenothiazines to the risk of breast cancer using data from a large case-control surveillance study.

METHODS

Since 1976, data have been collected from individuals with breast cancer, and with other diagnoses, in a hospital-based case-control surveillance study.[15] The current report includes women admitted to participating hospitals in Boston (1977-87), New York (1977-93), Baltimore (1977-85 and 1993-96), and Philadelphia (1977-96). Subjects were interviewed in hospital by trained nurse monitors, using a structured questionnaire that included demographic information and questions on medical and pregnancy history, family history of cancer, and consumption of alcohol, cigarettes, coffee, and tea. A lifetime history of medication use was obtained by asking about drug use for 40 indication categories. Antidepressant and phenothiazine use was elicited by questions about 'nerves', depression, tension, emotional disorders, psychiatric problems, and sleep problems. Antihistamine use was elicited by questions about use of drugs for allergies, breathing difficulties, fevers, coughs, and colds. For each episode of drug use reported, the drug name, starting date, frequency of use, and duration of use were recorded. Over the course of the study, 95% of patients targeted for interview have participated.

Cases

The present report includes 5814 women aged 18-69 years (median: 51 years), diagnosed with primary invasive breast cancer within the year before the current admission; individuals

with cancer-in-situ and those with a prior history of cancer (except nonmelanoma skin cancer) are excluded. Ninety-six percent were diagnosed within the six months before admission.

Controls

Two control series were selected from among the remaining female enrollments aged 18-69 years. The first group comprised 5095 women with primary malignancies of other organs (cancer controls). Individuals with tumors of the reproductive tract were excluded because these malignancies share some risk factors with breast cancer; in addition, antidepressant use has been linked to the risk of primary ovarian cancer.[16] As with the cases, the diagnosis was made within the previous year, and there was no history of any malignancy other than nonmelanoma skin cancer. The distribution of cancer sites was: 1899 (37%) gastrointestinal, 1058 (21%) bone, connective tissue, or skin, and 2138 (42%) other sites. The median age was 53 years.

The second control group consisted of women whose hospital admission resulted from a nonmalignant condition judged to be unrelated to antidepressant or antihistamine use (non-cancer controls). There was a large number of potential controls (19955). A sample of the total was selected at random to attain frequency-matching to the cases according to age (decade), region (4 categories), and date of interview (4 categories) at a ratio of 1:1. When there were insufficient subjects in a specific age-region-date stratum (particularly in New York for the older ages), individuals from another region were selected to achieve the matching ratio. Thus, the age distribution was identical to that of the cases, with a median of 51 years. Among the 5814 controls selected, 1019 subjects (18%) were admitted for trauma; 1151 (20%) for gastrointestinal disorders (e.g., cholelithiasis); 1540 (27%) for acute infections (e.g., pneumonia); 716 (12%) for

benign disorders of the female reproductive system (e.g., ovarian cyst), and 1388 (24%) for elective procedures (e.g., cataract removal).

Drug exposure

Use of tricyclic antidepressants, SSRIs, other antidepressants, phenothiazines, and antihistamines was defined as regular if it had taken place at least four days per week for a duration of at least four weeks. Individuals whose use of these drugs took place exclusively within the year before admission were kept in a separate category, because such use may not have preceded the onset of the cancer. Duration of regular use was summed over all lifetime episodes. First use was defined as the beginning of the first episode of exposure. Last use was defined as the end of the most recent episode of exposure.

Rates of regular drug use among the control subjects were examined within subgroups, adjusting for age and date of interview. The cancer controls were divided into two groups and the noncancer controls were divided into conditions for which hospital admission was obligatory (e.g., fractured femur) and other conditions for which admission may have been more elective (e.g., chronic cervicitis). Across these four groups, there was no tendency for the rates of regular drug use to be higher or lower in any particular subgroup of controls.

Analysis

Relative risk estimates (RR) and 95% confidence intervals (CI) were calculated using an SPSS-based unconditional multivariate logistic regression program. Variables included in the final multivariate models were factors found to be associated with breast cancer in these data. In addition to terms for SSRIs, tricyclic antidepressants, other antidepressants, antihistamines, and

phenothiazines, the model included terms for the following: age, region, race, religion, year of interview, age at first birth, body mass index [wt (kg)/ht(m)^2], history of cystic breast disease, current alcohol consumption, and number of lifetime hospitalizations.

RESULTS

Use of the drugs under study among cases, cancer controls, and noncancer controls is shown in Table 1. Tricyclics were the most commonly used antidepressants. For regular use, the RRs were 1.1 and 0.8 using the cancer controls and noncancer controls, respectively. The corresponding estimates for SSRIs were 1.6 and 1.5; neither estimate was statistically significant. For all of the other drug classes considered--other antidepressants, phenothiazines, and antihistamines--the RR estimates for regular use were close to 1.0 (range, 0.8-1.3). For "other" use of the drugs (i.e., nonregular use that began at least a year before admission), the estimates were, in all instances, compatible with 1.0. The estimates for phenothiazine use begun within the previous year were 0.9 and 6.9, respectively, using the two control groups; the latter estimate, highly significant, was accounted for by antinausea drugs that are used to counter the side effects of cancer treatment. All other estimates for use that began in the year before admission were compatible with 1.0. Nonregular use and use that commenced in the year before admission were not analyzed further. In all subsequent comparisons, the control groups were combined because the results were similar.

Table 2 lists the individual drugs taken regularly; for each drug group, the numbers in the rows are mutually exclusive. RRs were estimated for all drugs with at least 10 users in both cases and controls. Among the tricyclic antidepressants, amitriptyline was the most commonly used drug, with 88 cases and 209 controls [RR 0.8 (0.6-1.1)]; the RR estimates for imipramine

and doxepin were 1.1 and 1.2, respectively. Fluoxetine (Prozac) [RR 1.5 (0.8-2.6)] was the most frequently used SSRI (23 cases, 27 controls). The 'other antidepressant' group was accounted for mostly by unknown drugs, e.g., mood elevator, not otherwise specified. There were many individual drugs represented within the phenothiazine and antihistamine groups; among the former group, RR estimates for the individual drugs ranged from 0.6-1.4; none was statistically significant. Regarding the individual antihistamines, RRs for chlorpheniramine, doxylamine, and tripolidine,brompheniramine, terfenadine, and hydroxyzine ranged from 0.7-1.3.

In Table 3, regular drug use is stratified according to duration; the number of categories was determined by the numbers of users. There was no consistent pattern across duration of use for any of the drug classes. The risk estimates for various categories of duration of use of tricyclics varied from 0.5 to 1.3; the RR for ten or more years of use was 1.0 (0.5-1.8). Similarly, for phenothiazines and for antihistamines, there was a narrow range in the RR estimates (0.6-1.3) for the various categories of duration of use, and no tendency of direction in the estimates. None of these estimates was statistically significant. For SSRIs, the RR estimate was elevated, 2.1, for 1-2 years of use (1.0-4.4), but there was no further increase with longer duration of use; in fact, the point estimate was lower, 1.3, for $\geq$3 years of use.

In Table 4, the risk of breast cancer is examined according to the interval since last regular use. The relative risks for use that had continued into the year prior to hospitalization were 1.0, 1.1, 1.3, and 0.9 for tricyclics, other antidepressants, phenothiazines, and antihistamines, respectively. Estimates for other categories of interval since last use for these drug classes, ranging up to $\geq$10 years, varied from 0.5 to 1.5; there was no pattern in the relative risk estimates according to interval since last use. For SSRI, the relative risk was 1.8 (1.0-3.4)

for use that continued into the year before admission. The estimate for use that ended more than one year previously was 1.0, based on small numbers of users.

DISCUSSION

There was no statistically significant overall association between use of tricyclic antidepressants, SSRIs, other antidepressants, phenothiazines, or antihistamines and breast cancer risk in the present data. If the drugs of interest act to promote tumor growth, then one would expect to find an increased risk for more recent use. Recent use of tricyclic antidepressants, other antidepressants, phenothiazines, and antihistamines was not associated with breast cancer risk. There was an elevated RR estimate (1.8) for recent use of SSRIs that was of borderline statistical significance, but there was no consistent tendency for the RR estimate to increase with increasing duration of use. Information regarding long-term use of SSRIs was sparse: all of the exposed cases had taken SSRIs for less than five years.

The cases might have been more motivated to probe their memory for exposures that could be relevant to developing a malignancy. Thus, we included a control group with recently diagnosed malignancies because they might have been similarly motivated regarding recall of past drug use. In addition, the analysis was focussed on regular and recent use of these drugs, which should have been well remembered by cases and controls. Results were generally similar in comparisons using cancer or noncancer controls, suggesting that information bias was not a major problem.

Exposures that occurred exclusively during the 12-month period prior to admission were considered separately because such exposures may not have predated onset of the cancer or its diagnosis. This is an important issue for antidepressants, because early symptoms of as yet

undiagnosed cancer, or knowledge of the diagnosis, may be associated with depression (and increased use of antidepressants) among cases (and cancer controls), but not among controls without a malignancy. The increased relative risk for phenothiazine use during this period derived with the noncancer controls was probably accounted for by use subsequent to diagnosis and chemotherapy treatment.

It is possible that individuals who used antidepressants were more likely to be admitted to hospital. In addition, participation in the present study could have been associated with the exposures of interest, e.g., depressed subjects more likely to refuse the interview. However, participation rates among subjects targeted for interview were high. Morever, a comparison of regular drug use rates between the two control groups and within subgroups divided according to diagnosis revealed no material differences, and results obtained with the cancer and noncancer controls were similar. This suggests that the effort to select controls independent of the exposure was successful. Thus, the two groups of controls were combined in order to increase the power for subanalyses.

We believe confounding was adequately controlled. The multivariate model included terms for the major breast cancer risk factors and terms for factors associated with use of the drugs of interest. There was no evidence of important confounding, as the crude risk estimates were closely similar to those derived from multivariate models.

The present findings provide little support for the hypothesis that drugs that bind to intracellular histamine receptors increase the occurrence of breast cancer. The RRs for regular use of each of the drug groups examined were compatible with 1.0. However, the results for SSRIs were not entirely reassuring: While no overall association was observed and there was no evidence of a duration effect, there was a nonsignificantly elevated RR estimate for recent use,

consistent with the cancer promotion hypothesis. Despite the large number of subjects in the present study, over 5000 cases and twice as many controls, most were enrolled before SSRIs were approved and marketed; thus, there were fewer than 60 total users of these drugs available for the analysis. The frequency with which both the outcome (breast cancer) and the exposure (use of SSRI antidepressants) currently occur, make it important to examine the relation in further data, now that these drugs have been on the market for almost a decade.

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Table 1

Use of Antidepressants, Phenothiazines, and Antihistamines Among 5814 Women with Breast Cancer, 5095 Cancer Controls, and 5814 Noncancer Controls

Drug	Cases	Cancer controls		Noncancer controls	
		No.	Multivariate relative risk* (95% confidence interval)	No.	Multivariate relative risk* (95% confidence interval)
Tricyclic antidepressants					
Regular†	142	100	1.1 (0.8-1.5)	171	0.8 (0.6-1.0)
Other	62	42	1.0 (0.7-1.6)	55	1.0 (0.7-1.5)
First use <12 months	29	44	0.5 (0.3-0.8)	39	0.7 (0.4-1.2)
SSRI antidepressants					
Regular†	28	15	1.6 (0.8-3.2)	19	1.5 (0.8-2.8)
Other	3	1	---	1	---
First use <12 months	11	19	0.5 (0.2-1.1)	12	1.1 (0.5-2.6)
Other antidepressants					
Regular†	26	18	1.1 (0.6-2.0)	23	1.0 (0.6-1.9)
Other	21	12	1.6 (0.8-3.5)	13	1.7 (0.8-3.5)
First use <12 months	2	4	---	5	---
Phenothiazines					
Regular†	91	57	1.3 (0.9-1.9)	108	0.9 (0.6-1.1)
Other	83	68	0.8 (0.6-1.2)	92	0.7 (0.5-1.0)
First use <12 months	84	94	0.9 (0.7-1.3)	16	6.9 (3.9-12)
Antihistamines					
Regular†	147	131	0.9 (0.7-1.2)	164	0.8 (0.6-1.0)
Other	1590	1055	1.0 (0.9-1.1)	1323	1.1 (1.0-1.2)
First use <12 months	92	95	0.8 (0.6-1.2)	111	0.9 (0.7-1.3)

*Reference category is never use of each drug group.

†Use at least 4 days/week for at least 4 weeks, excluding use begun ≤1 year before admission.

Table 2 (1 of 2)

Individual Drugs* Taken Regularly by 5814 Cases and 10909 Controls

Drug group Drug	Cases	Controls	Multivariate relative risk (95% confidence interval)
Tricyclic antidepressants			
Amitriptyline	88	209	0.8 (0.6-1.1)
Imipramine	33	52	1.1 (0.7-1.7)
Doxepin	14	23	1.2 (0.6-2.5)
Desipramine	6	10	---
Nortriptyline	4	11	---
Protriptyline	1	0	---
Clomipramine	1	1	---
Amoxapine	2	1	---
Trimipramine	0	1	---
SSRI antidepressants			
Fluoxetine	23	27	1.5 (0.8-2.6)
Sertraline	4	4	---
Paroxetine	2	4	---
Other antidepressants			
Trazodone	4	9	---
Maprotiline	1	2	---
Bupropion	1	1	---
Venlafaxine	0	1	---
Antidepressant/Mood elevator, NOS	20	28	---
Phenothiazines			
Perphenazine	28	54	1.0 (0.6-1.6)
Trifluoperazine	20	26	1.4 (0.8-2.6)
Prochlorperazine	15	39	0.6 (0.3-1.2)
Chlorpromazine	22	30	1.4 (0.8-2.6)
Thioridazine	20	29	1.2 (0.6-2.1)
Fluphenazine	2	3	---
Mesoridazine	1	1	---
Promazine	1	0	---
Ethopropazine	0	2	---

*Subjects may have taken >1 drug in each group.

Table 2 (2 of 2)

Individual Drugs* Taken Regularly by 5814 Cases and 10909 Controls

Drug group Drug	Cases	Controls	Multivariate relative risk (95% confidence interval)
Antihistamines			
Chlorpheniramine	50	87	0.9 (0.6-1.3)
Doxylamine	23	42	0.9 (0.5-1.6)
Triprolidine	13	25	0.9 (0.5-1.9)
Brompheniramine	16	22	1.3 (0.6-2.5)
Terfenadine	13	26	0.8 (0.4-1.7)
Hydroxyzine	10	30	0.7 (0.3-1.4)
Diphenhydramine	9	41	---
Pyrilamine	8	14	---
Phenyltoxamine	5	10	---
Cyproheptadine	5	2	---
Dexbrompheniramine	4	14	---
Methapyrilene	4	12	---
Astemizole	4	6	---
Clemastine	4	2	---
Dimethindene	3	8	---
Dexchlorpheniramine	3	5	---
Antazoline	3	4	---
Promethazine	3	4	---
Pyrrobutamine	2	4	---
Carbinoxamine	2	2	---
Pheniramine	1	3	---
Dimenhydrinate	1	2	---
Tripelennamine	1	2	---
Thenyldiamine	1	1	---
Loratadine	0	2	---
Trimethobenzamide	0	2	---
Pyribenzamine	0	1	---
Trimeprazine	0	1	---
Antihistamine, NOS	5	9	---

*Subjects may have taken >1 drug in each group.

Table 3

Risk of Breast Cancer According to Duration of Regular Use of Antidepressants, Phenothiazines, and Antihistamines Among 5814 Breast Cancer Cases and 10909 Controls

Drug Duration (years)	Cases	Controls	Multivariate relative risk* (95% confidence interval)
Tricyclic antidepressants			
<1	36	81	0.7 (0.4-1.0)
1-4	76	111	1.3 (0.9-1.8)
5-9	11	44	0.5 (0.2-0.9)
≥10	19	35	1.0 (0.5-1.8)
SSRI antidepressants			
<1	5	9	1.3 (0.4-4.0)
1-2	16	15	2.1 (1.0-4.4)
≥3	7	9	1.3 (0.4-3.6)
Other antidepressants			
<1	10	19	0.8 (0.4-1.8)
1-4	11	14	1.2 (0.5-2.8)
≥5	5	8	1.3 (0.4-4.1)
Phenothiazines			
<1	23	53	0.6 (0.4-1.1)
1-4	36	54	1.2 (0.8-1.9)
5-9	15	23	1.3 (0.6-2.5)
≥10	17	35	1.2 (0.6-2.1)
Antihistamines			
<1	29	50	1.0 (0.6-1.6)
1-4	49	92	0.9 (0.7-1.4)
5-9	24	38	1.1 (0.7-1.9)
≥10	45	115	0.6 (0.4-0.9)

*Reference category is never use of particular drug.

Table 4

Risk of Breast Cancer According to Interval Since Last Regular Use of Antidepressants, Phenothiazines, and Antihistamines Among 5814 Breast Cancer Cases and 10909 Controls

Drug Interval since last use (years)	Cases	Controls	Multivariate relative risk* (95% confidence interval)
Tricyclic antidepressants			
<1	66	127	1.0 (0.7-1.4)
1-4	21	67	0.5 (0.3-0.9)
5-9	17	35	0.6 (0.3-1.2)
≥10	30	34	1.4 (0.8-2.4)
SSRI antidepressants			
<1	22	23	1.8 (1.0-3.4)
≥1	6	11	1.1 (0.4-3.1)
Other antidepressants			
<1	11	17	1.1 (0.5-2.4)
1-4	8	10	1.3 (0.5-3.4)
≥5	7	13	0.8 (0.3-2.3)
Phenothiazines			
<1	44	70	1.3 (0.9-2.0)
1-4	8	25	0.5 (0.2-1.2)
5-9	17	19	1.5 (0.8-3.1)
≥10	21	47	0.7 (0.4-1.3)
Antihistamines			
<1	93	182	0.9 (0.7-1.2)
1-4	21	42	0.8 (0.4-1.3)
5-9	8	18	0.8 (0.3-1.9)
≥10	18	30	1.0 (0.6-1.9)

*Reference category is never use of particular drug.